

INTERNATIONAL COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Assistant Commissioner for Patents
United States Patent and Trademark
Office
Box PCT
Washington, D.C. 20231
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 19 November 1999 (19.11.99)	Applicant's or agent's file reference SUN-84PCT
International application No. PCT/US99/06573	Priority date (day/month/year) 26 March 1998 (26.03.98)
International filing date (day/month/year) 25 March 1999 (25.03.99)	
Applicant HSUEH, Aaron, J., W. et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:

20 October 1999 (20.10.99)

☐ in a notice effecting later election filed with the International Bureau on:2. The election ☒ was☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

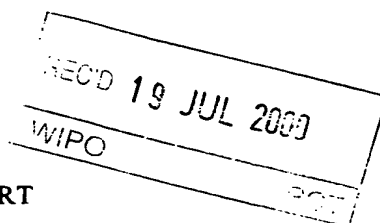
<p>The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland</p> <p>Facsimile No.: (41-22) 740.14.35</p>	<p>Authorized officer Kiwa Mpay</p> <p>Telephone No.: (41-22) 338.83.38</p>
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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)



Applicant's or agent's file reference SUN-84PCT	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/US99/06573	International filing date (day/month/year) 25 MARCH 1999	Priority date (day/month/year) 26 MARCH 1998
International Patent Classification (IPC) or national classification and IPC Please See Supplemental Sheet.		
Applicant THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 9 sheets.

☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 0 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of report with regard to novelty, inventive step or industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand 20 OCTOBER 1999	Date of completion of this report 13 JUNE 2000
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Authorized officer David L. FITZGERALD
Facsimile No. (703) 305-3230	Telephone No. (703) 308-0196

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US99/06573

I. Basis of the report**1. With regard to the elements of the international application:***☒ the international application as originally filed☒ the description:

pages 1-26

pages NONE

pages NONE

, as originally filed
, filed with the demand
, filed with the letter of☒ the claims:

pages 27-29

pages NONE

pages NONE

pages NONE

, as originally filed
, as amended (together with any statement) under Article 19
, filed with the demand
, filed with the letter of☒ the drawings:

pages 1-8

pages NONE

pages NONE

, as originally filed
, filed with the demand
, filed with the letter of☒ the sequence listing part of the description:

pages 1-11

pages NONE

pages NONE

, as originally filed
, filed with the demand
, filed with the letter of**2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.**

These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).☐ the language of publication of the international application (under Rule 48.3(b)).☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).**3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:**☒ contained in the international application in printed form.☒ filed together with the international application in computer readable form.☐ furnished subsequently to this Authority in written form.☒ furnished subsequently to this Authority in computer readable form.☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.☒ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.**4. ☒ The amendments have resulted in the cancellation of:**☒ the description, pages NONE☒ the claims, Nos. NONE☒ the drawings, sheets/fig NONE**5. ☒ This report has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).****

* Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).

**Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US99/06573

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been and will not be examined in respect of:

☐ the entire international application.

☒ claims Nos. 1-11, as they read on LGR-5 and -7; and 12-18

because:

☐ the said international application, or the said claim Nos. _ relate to the following subject matter which does not require international preliminary examination (*specify*).

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. _ are so unclear that no meaningful opinion could be formed (*specify*).

☐ the claims, or said claims Nos. _ are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for said claims Nos. (See Attached).

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US99/06573

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**1. statement**

Novelty (N)	Claims <u>1-4, 7-11</u>	YES
	Claims <u>5, 6</u>	NO
Inventive Step (IS)	Claims <u>1-4, 7-11</u>	YES
	Claims <u>5, 6</u>	NO
Industrial Applicability (IA)	Claims <u>1-11</u>	YES
	Claims <u>none</u>	NO

2. citations and explanations (Rule 70.7)

Claims 5 and 6 lack novelty under PCT Article 33(2) as being anticipated by FUJIWARA et al (GenBank D61947). The database record describes an EST (*i.e.*, a partial cDNA) in which residues 189-238 are identical to the sequence complementary to residues 832-881 of instant SEQ ID NO: 1.

Claims 1-4 and 7-11 meet the criteria for novelty and inventive step set forth in PCT Article 33(2) and 33(3). None of the prior art references describing EST fragments of the instant LGR-4 sequence teaches or fairly suggests the nature or distinguishing structural features of any full-length clone or a coresponding polypeptide.

Claims 1-11 meet the criteria for industrial applicability set forth in PCT Article 33(4) as LGR-4 finds use at least in the identification of the instantly described tissue types which express it.

----- NEW CITATIONS -----

Database GenBank, National Library of Medicine (Bethesda, MD, US) Entrez browser, acc. no. D61947, FUJIWARA, T., et al., "HUM225E05B Clontech human aorta polyA+ mRNA (#6572) Homo sapiens cDNA clone GEN-225E05 5', mRNA sequence," 29 August 1995.

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

Claims 1, 3, and 8-11 are objected to under PCT Rule 66.2(a)(v) as lacking clarity under PCT Article 6 because they are indefinite.

All of the noted claims are indefinite with respect to the scope of subject matter embraced by the term 'mammalian LGR4 protein.' Although the description provides that an 'LGR4' protein will exhibit at least about 80% identity with the exemplified sequence, it provides no teachings by which the skilled artisan would understand the degree of structural relationships between LGR proteins found in various mammalian species. The description does not describe the genus of polypeptides which are both at least about 80% identical to instant SEQ ID NO: 2 and which are identical in structure to polypeptides found in mammals. Alternatively phrased, the skilled artisan, if presented with a polypeptide of, *e.g.*, 85% identity to instant SEQ ID NO: 2, could not determine by comparison with the present disclosure whether or not the polypeptide was a 'mammalian' species as claimed. Claims 1, 3, and 8-11 thus do not convey with particularity and distinction the metes and bounds of the subject matter claimed.

Claim 3 is vague and indefinite with respect to the use of the term 'substantially identical.' The description does not employ or define the term in question; only "substantial similarity" is discussed. Because it is not clear what degree of structural relationship is required to establish 'substantial identity,' the scope of the subject matter embraced by claim 3 cannot be unambiguously ascertained.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US99/06573

Supplemental Box

(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

Sheet 10

CLASSIFICATION:

The International Patent Classification (IPC) and/or the National classification are as listed below:

IPC(7): C07K 14/705; C12N 15/12, 15/63, 15/70, 15/79 and US Cl.: 530/350; 435/69.1, 252.3, 254.11, 320.1, 325

I. BASIS OF REPORT:

5. (Some) amendments are considered to go beyond the disclosure as filed:

NONE

III. NON-ESTABLISHMENT OF REPORT:

No international search report has been established for claim numbers 1-11, as they read on LGR-5 and -7; and 12-18.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/06573

A. CLASSIFICATION OF SUBJECT MATTER IPC(6) :C07K 14/705; C12N 15/12, 15/63, 15/70, 15/79 US CL :530/350; 435/69.1, 252.3, 254.11, 320.1, 325 According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) U.S. : 530/350; 435/69.1, 252.3, 254.11, 320.1, 325 Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) APS, Biosis, Medline, WPI search terms: G-protein coupled receptor, Leucine rich repeats, Gonadotropin receptor, Thyrotropin receptor		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,614,363 A (CONE) 25 March 1997, entire document.	1-11
X, P ----- Y, P	US 5,858,716 A (ELSHOURBAGY et al.) 12 January 1999, columns 20-30, entire document.	11 ----- 1-10
X -- Y	HWANG et al. Analysis of Expressed Sequence Tags from a Fetal Human Heart cDNA Library. Genomics. 1995, Vol. 30, pages 293-298, entire document.	5, 7, 11 ----- 1-4, 6, 8-10
<input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> See patent family annex.		
* Special categories of cited documents: *A* document defining the general state of the art which is not considered to be of particular relevance *B* earlier document published on or after the international filing date *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) *O* document referring to an oral disclosure, use, exhibition or other means *P* document published prior to the international filing date but later than the priority date claimed	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art *Z* document member of the same patent family	
Date of the actual completion of the international search 11 JUNE 1999		Date of mailing of the international search report 02 AUG 1999
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230		Authorized officer <i>D. Lawrence Teng</i> Sally P. Teng Telephone No. (703) 308-0196

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US99/06573

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING

This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I, claims 1-11, drawn to nucleic acids encoding LGR4, the LGR4 polypeptide, and method of using the LGR4 nucleic acid.

Group II, claims 1-11, drawn to nucleic acids encoding LGR5, the LGR5 polypeptide and method of using the LGR5 nucleic acid.

Group III, claims 1-11, drawn to nucleic acid encoding LGR6, the LGR6 polypeptide, and method of using the LGR6 nucleic acid.

Group IV, claims 12 and 13, drawn to antibody that binds to LGR4.

Group V, claims 12 and 13, drawn to antibody that binds to LGR5.

Group VI, claims 12 and 13, drawn to antibody that binds to LGR7.

Group VII, claims 14-17, drawn to transgenic animal model containing an altered LGR4 gene.

Group VIII, claims 14-17, drawn to transgenic animal model containing an altered LGR5 gene

Group IX, claims 14-17, drawn to transgenic animal model containing an altered LGR7 gene

Group X, claim 18, drawn to a method of screening for a ligand for LGR4.

Group XI, claim 18, drawn to a method of screening for a ligand for LGR5.

Group XII, claim 18, drawn to a method of screening for a ligand for LGR7.

Each of the claims 1-18 is in three different groups because LGR4, LGR5, and LGR7 are structurally and functionally distinct polypeptides.

The inventions listed as Groups I-XII do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: The special technical feature of Group I is the nucleic acid sequence encoding LGR4. The special technical feature of Group II is the nucleic acid sequence encoding LGR5. The special technical feature of Group III is the nucleic acid sequence encoding LGR7. The special technical feature of Group IV is the antibody that binds to LGR4 but does not have the amino acid sequence of LGR4. The special technical feature of Group V is the antibody that binds to LGR5 but does not have the amino acid sequence of LGR5. The special technical feature of Group VI is the antibody that binds to LGR6 but does not have the amino acid sequence of LGR6. The special technical feature of Group VII is a transgenic animal containing an altered LGR4 gene. The special technical feature of Group VIII is a transgenic animal containing an altered LGR5 gene. The special technical feature of Group IX is a transgenic animal containing an altered LGR7 gene. The special technical feature of Group X is a method of screening for a ligand that binds LGR4. The special technical feature of Group XI is a method of screening for a ligand that binds LGR5. The special technical feature of Group XII is a method of screening for a ligand that binds LGR7. The special technical feature of each group is not the same or does not correspond to the special technical feature of any other group because the products of Groups I-IX are structurally and functionally distinct and the methods of Groups I-III and X-XII are distinct methods of using different starting reagent for accomplishing different goals. The groups are not linked by a special technical feature within the meaning of PCT Rule 13.2 so as to form a single inventive concept.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/06573

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X, P	HSU et al. Characterization of Two LGR Genes Homologous to Gonadotropin and Thyrotropin Receptors with Extracellular Leucine-Rich Repeats and a G Protein-Coupled, Seven Transmembrane Region. Molecular Endocrinology. December 1998, Vol. 12, No. 12, pages 1830-1845, especially pages 1831-1837.	1-11